Additive Effects of Sonic Hedgehog and Nell-1 Signaling in Osteogenic versus Adipogenic Differentiation of Human Adipose-Derived Stromal Cells.

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Public Summary:
With the increasing prevalence of obesity in our society, fat tissue is all too abundant. Researchers at University of California, Los Angeles have pointed out a silver lining to this dark cloud. Fat tissue is also rich in stem cells, most commonly termed 'adipose-derived stromal cells.' These cells, with the appropriate molecular cues, are able to form other tissue types, including bone, muscle, cartilage, among others. In the laboratory of Dr. Soo, researchers are honing down on the optimum combination of molecular cues necessary for converting fat into bone tissue. These include combining two potent growth factors: Sonic Hedgehog and Nell-1. Nell-1 is a molecule of interest for the Soo laboratory, discovered to have osteogenic (bone-forming) activity by its presence in a childhood disease of overzealous bone formation (craniosynostosis). As they report in Stem Cells and Development, either Sonic Hedgehog (Shh) or Nell-1 are able to coax these stem cells to form bone. When added in combination, these two growth factors show a robust and additive enhancement over either alone. The authors went on to determine if there was any intersection between these two signaling pathways. In fact, data suggest that interfering with the Shh pathway interrupts Nell-1 from having its usual effect. James et al. and others argue that fat tissue is an attractive source of stem cells for future efforts in tissue regeneration. This recent publication suggests a new bone tissue-inducing 'cocktail' of growth factors for skeletal tissue engineering.

Scientific Abstract:
A theoretical inverse relationship exists between osteogenic (bone forming) and adipogenic (fat forming) mesenchymal stem cell differentiation. This inverse relationship in theory partially underlies the clinical entity of osteoporosis, in which marrow mesenchymal stem cells (MSCs) have a preference for adipose differentiation that increases with age. Two pro-osteogenic cytokines have been recently studied which each also possesses anti-adipogenic properties: Sonic Hedgehog (SHH) and NELL-1 proteins. In the present study, we assayed the potential additive effects of the biologically active N-terminus of SHH (SHH-N) and NELL-1 protein on osteogenic and adipogenic differentiation of human primary adipose-derived stromal cell (hASCs). We observed that both recombinant SHH-N and NELL-1 protein significantly enhanced osteogenic differentiation and reduced adipose differentiation across all markers examined (alkaline phosphatase, Alizarin red and Oil red O staining, and osteogenic gene expression). Moreover, SHH-N and NELL-1 directed signaling showed additive effects on the pro-osteogenic and anti-adipogenic differentiation of hASCs. NELL-1 treatment increased Hedgehog signaling pathway expression; co-application of the Smoothened antagonist Cyclopamine reversed the pro-osteogenic effect of NELL-1. In summary, Hedgehog and Nell-1 signaling show additive effects on the pro-osteogenic and anti-adipogenic differentiation of ASCs. These studies suggest that the combination cytokines SHH-N+NELL-1 may represent a viable future technique for inducing osteogenic differentiation of MSCs.